REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Official Action dated January 22, 2009. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 17, 21–25, 34 and 42-50 are under consideration in this application. Claims 1-16, 18-20, 26–33 and 35–41 stand canceled without prejudice or disclaimer. Claims 17 and 21 are amended, as set forth above, to correct minor typographical errors. New claims 42-50 have been added. The claim amendments including the addition of new claims 42-50 have been made to more particularly define and distinctly claim Applicant's invention. The specification provides full support for new claims 42-50; for instance, pages 14-16 of the specification provides detailed description of exemplary fish protein hyrolyzate. All the amendments to the claims are supported by the specification and no new matter is believed to have been added.

Claim Rejections - 35 USC § 112

Claims 17, 21–25 and 34 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable a method of preventing fatty acid liver, a method of preventing hypercholesterolemia, and a method of preventing hyperhomocysteinemia. The Examiner alleges that the quantity of experimentation required would be large due to the variation between individuals and underlying cause of each condition; that the art is allegedly unpredictable with regard to the cause and mechanism of development of fatty liver, hypercholesterolemia, and hyperhomocysteinemia; and that there is lack of guidance in the specification with regard to teaching how to prevent "all cases of fatty liver, hypercholesterolemia, and hyperhomocysteinemia." Applicant respectfully disagrees and traverses as follows.

The specification provides clear guidance and working examples that enable a person skilled in the art how to make and use the claimed invention for both treating and preventing fatty acid liver, hypercholesterolemia, and hyperhomocysteinemia. For instance, Example 2 describes results which clearly indicate that the fish protein hydrolysate (FPH) decreases the levels of cholesterol in the plasma and is effective as a

cholesterol lowering agent. Example 3 shows that FPH induces a lowering of the concentration of triacylglycerols in the liver of about 50%. This indicates that the FPH of the present invention is effective as a lipid lowering agent for the prevention of fatty liver.

As evident from Example 5, the FPH of the present invention is also effective in increasing the mitochondrial β-oxidation. Increased fatty acid oxidation is an important factor behind the lipid lowering effect of FPH. The increased fatty acid catabolism will decrease the amount of fatty acids available for esterification, and thereby reduce the production and secretion of VLDL by the liver. Moreover, Example 7 indicates that the FPH of the present invention is effective for lowering the concentration of homocysteine in plasma, and would thus be expected to reduce the incidence of hyperhomocysteinemia. These examples are further evidence of the preventive effects of FPH.

On page 2, paragraph 2, of the specification, Applicant describes that the Fish Protein Hydrolyzate (FPH) lowers the concentration of plasma cholesterol, homocysteine and hepatic triacylglycerols. Since elevated levels of these compounds are implicated in the various disease states, a person skilled in the art would reasonably conclude that the claimed FPH would have a "preventive and/or therapeutic effect" on stenosis, atherosclerosis coronary heart disease, thrombosis, myocardial infarction, stroke and fatty liver. See page 2, paragraph 2. See also page 2, paragraphs 4 and 5 and page 3, paragraphs 1 and 2. Moreover, as mentioned on page 3, paragraph 3, the specification clearly describes that hyperhomocysteine levels can be established before the above indicated diseases are manifested. Since the administration of the FPH has a general homocysteine lowering effect, the FPH is particularly suited for preventing the onset of, and lowering the risk for the claimed diseases.

On page 5, paragraph 5 of the Specification, Applicant explicitly defined "prevention" as inviting the use of FPH prior to the onset of the condition making the compounds of the present invention eminently usable as a prophylactic agent. The Examiner is further referred to the Examples and Tables 1 – 3 where Applicant conclusively demonstrates both the preventive and therapeutic benefits of the claimed compound and or composition.

Applicant by their disclosure and examples, have shown to a reasonable level of scientific and therapeutic certainty that their FPH have preventive and therapeutic benefits as described and claimed. The requirement that Applicant must show that the agent would prevent any and all cases and causes of the claimed disorders, is with

all due respect, unreasonable and beyond the requirements of the law. In the first place, there is no known therapeutic or preventive modality, aid, compound or composition which is 100 percent effective in 100 percent of all cases in 100 percent of the time. Even as a purely idiosyncratic matter, patients have been known to be resistant to generally accepted and well proven treatments or preventive aid but that does not invite a requirement that a specification bearing patent applications for such must show "prevention" to the unreasonable degree required by the Examiner. The science and art in this area require demonstration of efficacy to a statistically significant level and nothing more.

Moreover, it does appear to the Applicant that the Examiner is confusing the causative agent and the disease. In this particular area of practice, the presence of the causative agent precedes the disease itself. In other words, elevated levels of cholesterol in the plasma is not co-terminus with the disease of hypercholesterolemia which is caused by elevated levels of cholesterol in the plasma. It follows therefore that decreasing the levels of the claimed plasma cholesterol, homocysteine and hepatic triacylglycerols in the blood will prevent manifestation of the claimed disease conditions as well as being beneficial for the treatment of the claimed disease conditions. The specification provides clear guidance that the FPH of the present invention has both a prophylactic and a treatment utility and there is no basis for maintaining the present rejection.

Therefore, based at least on the clear guidance in the specification, and the numerous working examples provided by Applicant, it would not require undue experimentation to practice the invention as claimed. Accordingly withdrawal of this ground for rejection is respectfully requested.

Rejections under 35 U.S.C. §103(a)

Claims 17, 21 – 25 and 34 stand rejected under 35 U.S.C. §103 (a) as being unpatentable over Aoyama et al. (Biosci. Biotech. Biochem., 2000, vol. 64, no. 12, p. 2594-2600) in view of Nielson (US 2002/0182290) and Bergeron et al. (J. Nutrition, 1992, vol. 122, p. 1731-1737) and Liceaga-Gesualdo et al. (J. Food Science, 1999, vol. 64, no. 6, p. 1000-1004) and further in view of Van Guldener and Stehouwer (Expert Opinion Pharmacotherapy, 2001, vol. 2, no. 9, p 1449-1460) and further in view of Cahu et al. (Aquaculture, 2001, vol. 200, p. 161-180).

The Examiner alleges that Aoyama et al. teach a method of treating hypercholesterolemia by administering a composition comprising milk whey protein hydrolysate and a composition

comprising soy protein hydrolysate. The Examiner acknowledges that Aoyama et al. fails to teach administration of an enzyme treated fish protein hydrolysate, and fails to teach lowering the concentration of plasma homocysteine and hepatic triacylglycerols.

The Examiner alleges that Nielson teaches a composition comprising an enzyme treated fish protein hydrolysate material, and that Nielson allegedly teaches hydrolyzing fish flesh remnants with a protease enzyme to yield a hydrolysate.

Applicant maintains that Aoyama et al. and Nielson are not even properly combinable. One of ordinary skill in the art would have clearly understood that "each type of food protein has a unique molecular structure that determines its functional properties (...)", and "the functional and structural properties of food proteins thus vary tremendously (...)" (Kristisson and Rasco, previously cited; p. 44, 1st col., 4th and 5th paragraphs). Moreover, "enzymatic hydrolysis of fish proteins generates a mixture of free amino acids, di-, tri-, and oligopeptides, increases the number of polar groups and the solubility of the hydrolyzate, and therefore modifies functional characteristics of the proteins, improving their functional characteristics and bioavailability. The choice of substrate and proteases employed and the degree to which the protein is hydrolyzed affect the physicochemical properties of the resulting hydrolyzate (Kristisson and Rasco, previously cited; p. 44, 1st col., 4th and 5th paragraphs, and p. 64, 2nd col., 1st paragraph). To that extent, the deficiency in Aoyama et al. in failing to teach the use of fish protein or fish protein hydrolyzate, but instead teaching whey and soy protein hydrolysates, cannot simply be cured by combination with another, unrelated reference teaching the use of fish protein hydrolyzate, since it is clear, as indicated above, that completely unrelated proteins are, in fact, markedly different substrates with widely varying functional and structural properties. There would simply be no motivation to use fish protein hydrolysate in the method of Aoyama et al., based on the unrelated teaching of Nielson.

Even assuming, *arguendo*, that Aoyama et al. and Nielson could be properly combined, the combined references still fail to teach each and every element of the claimed invention. Namely, the combined references fail to teach either a method of preventing, or a method of treating, fatty liver, hypercholesterolemia, or hyperhomocysteinemia by administering to an animal in need of such treatment, a pharmaceutical or nutritional composition comprising an enzyme treated fish protein hydrolyzate material for lowering the concentration of plasma cholesterol, homocysteine and hepatic triacylglycerols.

The Examiner alleges that Bergeron et al. provides further motivation to use fish protein hydrolysate in the method of Aoyama et al., because Bergeron et al. allegedly teaches feeding

fish protein, combined with either corn oil or coconut oil, which allegedly resulted in higher HDL cholesterol concentrations, in comparison with soybean protein. The Examiner has previously acknowledged that Bergeron et al. do not teach an enzyme treated FPH (page 5, March 27, 2008 Office Action).

Bergeron et al. and Aoyama et al. are not even properly combinable. As discussed above, the deficiency in Aoyama et al. in failing to teach the use of fish protein or fish protein hydrolyzate – but instead teaching whey and soy protein hydrolysates -- cannot simply be cured by combination with another, unrelated reference teaching the use of fish protein, since it is clear, as indicated above, that completely unrelated proteins are, in fact, markedly different pharmacologically speaking, with regard to both functional and structural properties.

Moreover, there would simply have been no motivation at the time of the invention to use fish protein in the method of Aoyama et al., based on the unrelated teaching of Bergeron et al. Instead, as acknowledged by the Examiner, Bergeron et al. teaches feeding fish protein combined with either corn oil or coconut oil. Bergeron et al. fails to teach or suggest that lowering the concentration of plasma cholesterol, homocysteine and hepatic triacylglycerols are mediated by administration of a composition comprising an enzyme treated *fish protein hydrolyzate material, i.e., in the absence of corn oil or coconut oil.* As acknowledged by the Examiner, Bergeron et al. teaches that dietary proteins and lipids modulate triglyceride and cholesterol concentrations. Whereas Bergeron et al. conclude from their experiments that "current data indicates that fish protein can produce variable effects on serum total cholesterol concentrations depending in part on the amount and origin of the dietary lipid with which it is combined," nothing in Bergeron nor the asserted combination suggests, teaches nor would otherwise make it obvious to use fish protein uncombined with dietary lipid for prophylactic or therapeutic uses in the treatment or prevention of fatty liver, hypercholesterolemia or hyperhomocysteinemia. In particularly, Bergeron et al. teach variable and indeterminate effect of fish protein combined with dietary lipid on serum total cholesterol and do not teach the cardioprotective effect, if any, of fish protein hydrolyzate. It is clear that Bergeron et al. fails to teach or suggest the claimed pharmacologic effects of a composition comprising enzyme treated fish protein hydrolyzate material. The teachings of Bergeron et al. therefore clearly do not cure the deficiencies of Aoyama et al.

None of the additional cited references remedy the deficiencies of Aoyama et al., either alone or in view of Nielson and Bergeron et al.

The Examiner alleges that Liceaga-Gesualdo teaches enzymatic treatment of fish protein

which releases methionine. However, Liceaga-Gesualdo fails to teach or suggest the claimed effects of a composition comprising enzyme treated fish protein hydrolyzate material. Moreover, the present invention as claimed is not based on a methionine restriction in order to obtain a reduction of homocysteine. In addition, for reasons already discussed above, Liceaga-Gesualdo fails to cure the deficiencies of Aoyama et al. The deficiency in Aoyama et al. in failing to teach the use of fish protein or fish protein hydrolyzate, but instead teaching whey and soy protein hydrolysates, cannot be cured by combination with an unrelated reference teaching the use of fish protein, since the functional and structural properties of fish protein versus whey and soy protein are completely different.

The Examiner alleges that Van Guldener teaches reducing plasma homocysteine concentration by dietary means, that is, by methionine restriction. However, as noted above, the present invention as claimed is not based on a methionine restriction in order to obtain a reduction of homocysteine. Thus, not only are the cited references not combinable with Van Guldener, the combined art fails to teach the prophylactic and/or therapeutic use of fish protein hydrolyzate as claimed.

Lastly, the Examiner alleges that Cahu et al. teaches growth of salmon fry was enhanced by replacing the amino acid nitrogen in a fish meal based diet by fish protein hydrolysate. The claims are not directed to enhanced growth mediated by fish protein hydrolysate. Cahu et al. fails to teach or suggest the prophylactic and/or therapeutic use of fish protein hydrolyzate as claimed, and thus Cahu et al. fails to remedy the deficiencies of the other cited references.

It is generally known that fish oil found in fish fillets is universally rich in omega 3 fatty acids and is cardioprotective making it counterintuitive for cardio-prophylactic and cardiotherapeutic uses to attempt to use enzymatic hydrolyzates of fish protein for the claimed uses since that process would have the effect of substantially stripping the fish protein of supposedly beneficial omega 3 fatty acids. That such hydrolyzate would have the effect shown and claimed in the instant invention, despite being substantially stripped of omega-3-fatty acids, is totally unexpected. See page 15 of the Specification. Such unexpected and unobvious effect could not have been cured by the cited references which fail to teach or suggest the claimed clinical uses for FPH or by Bergeron which was concerned with the beneficial uses of fish protein combined with dietary lipids. Assuming for the sake of argument, that despite being biochemically and pharmacologically distinct, the Examiner insists that fish protein and FPH would function in substantially the same way, it cannot also be held judging from the remarkable and surprising effects disclosed in the specification that their pharmacologic action in terms of

treating the claimed disease condition is substantially similar.

The Examiner is reminded that impermissible hindsight precludes the use of the novel medical uses of this invention to deny patentability to the same invention that informed the hindsight. Nor is this the "obvious to try" situation contemplated by the Supreme Court in KSR because Bergeron's fish protein/dietary lipid is a far cry from enzymatic fish protein hydrolyzate being used for prophylactic and/or therapeutic applications for fatty liver, hypercholesterolemia and hyperhomocysteinemia. Applicant is merely claiming that because it was unexpected and unobvious to attain the results disclosed, that they deserve to be rewarded for their contribution to the pharmaceutical arts, no more and no less, for discovering that fish protein hydrolyzate can be used to treat or prevent hyperhomocysteinemia, fatty liver, and hypercholesterolemia.

In fact, Bergeron suggests that the lipoprotein lipase (LPL) activity is a determinant for the fish-protein induced decrement in VLDL triglycerides and concomitant rise in HDL cholesterol in rabbits (p. 1736, 2nd col., 2nd paragraph). Bergeron further discusses that a fish protein induced rise in lipoprotein lipase activity may result from an increase in the concentration of apo C-II as cofactor, which is considered important for full activity expression of the LPL. One skilled in the art who is familiar with mechanism for enzymatic reactions would not assume that Bergeron's unhydrolysed proteins would have the same effect as a fish protein hydrolyzate on an enzymatic reaction, even if they came from the same origin/fish. As demonstrated by Example 4 ([0059]-[0061]) in the specification of the present invention, the administration of FPH to rats inhibits the Acyl-CoA:cholesterol transferase (ACAT) to 0.035 nmol/mg/min, which catalyses the reaction in which fatty acyl-CoA is esterified to cholesterol, while unhydrolysed proteins (i.e., casein) only inhibits the ACAT to 0.05 nmol/mg/min. As such, unhydrolyzed protein does not necessarily deliver the same mechanism and as significant beneficial effect on cholesterol as FPH (Fig. 3).

For at least the fact that the asserted combination is not only improper but fails to teach all the elements of the instant invention, and for at least the fact that the results obtained and disclosed in the invention are unexpected and unobvious to try, Applicant respectfully requests that the Examiner reconsider and withdraw this grounds for rejection.

Conclusion

In view of all the above, clear and distinct differences as discussed which exist between the present invention as claimed and the prior art reference upon which the rejections in the Office Action rely, Applicant respectfully contends that the prior art references cannot render the present invention obvious. Rather, the present invention as a whole is distinguishable, and thereby allowable over the prior art.

Favorable reconsideration of this application is respectfully solicited. Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of the above-captioned application, the Examiner is invited to contact the Applicant's undersigned representative at the address and phone number indicated below.

Respectfully submitted,

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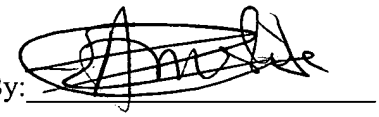
By: 

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Date: 07/21/2009

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